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REVIEW



Recent advances in alleviating food allergenicity through fermentation

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ABSTRACT

The increasing prevalence of food allergies is a significant challenge to global food health and safety. Various strategies have been deployed to decrease the allergenicity of food for preventing and reducing related disorders. Compared to other methods, fermentation has unique advantages in reducing the allergenicity of food and may represent a new trend in preventing food-induced allergies. This review introduces the characteristics of allergens in various foods, including shellfish, soy, peanut, milk, tree nut, egg, wheat, and fish. The mechanism and pathological symptoms of allergic reactions are then summarized. Furthermore, the advantages of fermentation for reducing the allergenicity of these foods and preventing allergies are evaluated. Fermentation is an efficient approach for reducing or eliminating food allergenicity. Simultaneously, it improved the nutritional value and physicochemical properties of food materials. It is conceivable that a combination of mixed strain fermentation with additional processing, such as heat treatment, pulsed light, and ultrasonication, will efficiently reduce the allergenicity of various foods and preserve their unique taste and nutritional components, providing significance for patients with allergies.

KEYWORDS

Food allergy; fermentation; food allergens; allergenicity

Introduction

Food allergies are a major public health problem (Chizoba Ekezie, Cheng, and Sun 2018) that affects 1% to >10% of the general population, depending on the geographical area and age of the patients (Gray et al. 2014). Of note, the prevalence of food allergies in children is usually higher than in the general population, reaching 5%-12.6% in some countries (Acker et al. 2017; Devdas et al. 2018; Manuyakorn and Tanpowpong 2019; Savage and Johns 2015) (Figure 1A). It has also been reported that the prevalence of food allergies increased by approximately 69% between 1999 and 2014, reaching nearly 8% in US children (Acker et al. 2017; Manuyakorn and Tanpowpong 2019; Yu, Freeland, and Nadeau 2016) (Figure 1B). Analyses have also revealed that more than 170 foods can cause allergenic reactions in humans, but 90% of these allergies are induced by allergens from 8 major foods, including shellfish, soy, peanut, milk, tree nut, egg, wheat and fish (Chizoba Ekezie, Cheng, and Sun 2018; Pi et al. 2019; Tammineedi and Choudhary 2014). A survey in 2017 revealed that the most common food allergens were shellfish (0.9% of the total survey population), fruit and vegetable (0.7%), milk (0.5%), and peanut (0.5%) (Acker et al. 2017) (Figure 1C). Thus, shellfish, milk, peanuts, tree nuts, and eggs account for more than 65% of food allergies. However, milk, peanut, wheat, egg and tree nut are the most common sources of allergens in children (Ricci et al. 2019; Savage and Johns 2015). While

allergies to milk, egg, soy, and wheat are often outgrown, allergies to peanuts, shellfish, tree nuts, and fish usually persist (Valenta et al. 2015; Wiparat and Pornthep 2019).

Food allergies can cause urticaria, rhinitis, swelling, anaphylactic shock, death, etc. (Acker et al. 2017; Pi et al. 2019). Allergen avoidance is the first choice and best option for people with food allergies because specific immunotherapy is currently unavailable (Fu et al. 2019; Wiparat and Pornthep 2019). However, allergen avoidance is almost impossible. Therefore, it appears that reducing the allergenicity of food materials through food processing has become an increasingly attractive alternative for preventing food allergies. At present, a variety of strategies have been deployed to reduce food allergenicity, including physical (heat, radiation, pulsed light, cold plasma, ultrasonication, and high-pressure treatments), chemical (glycosylation, magnetic-bead adsorption, and acid treatment), and biological (fermentation, enzyme catalysis, and genetic engineering) treatments (Chizoba Ekezie, Cheng, and Sun 2018; Pi et al. 2019). Many of the methods are limited by unwanted effects on foods, poor safety, and high cost (Pi et al. 2019). Interestingly, fermentation can significantly decrease the allergenicity of foods without these shortcomings. It also improves the physicochemical properties and nutritional values of food and reduces the sensitivity of the human body to food allergens (Chen et al. 2012; El-Ghaish et al. 2011).

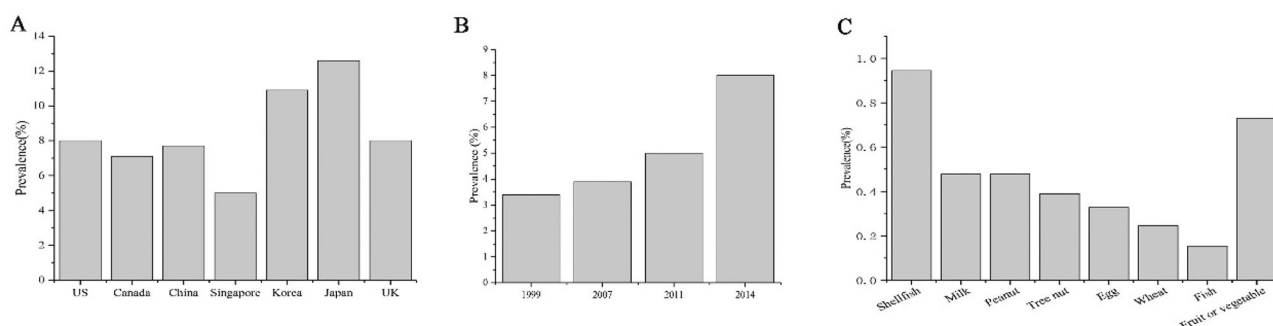


Figure 1. Current situation of food allergy. A. The prevalence of food allergy in children among some countries. B. The prevalence of food allergy in US children for 1999-2014. C. The prevalence of each food allergy in total survey population.

Therefore, we provide an up-to-date review of recent progress on fermentation for alleviating food-induced allergies.

Fermentation to reduce the allergenicity of foods

Peanut

Peanut is a nutrient-rich popular food rich in proteins (25%), unsaturated fatty acids (45%-50%), vitamins (especially B and E), fiber, and minerals (Ozias-Akins and Breiteneder 2019; Pi et al. 2019). It has significant benefits in preventing cardiovascular disease and controlling adiposity (Pi et al. 2019). However, peanut allergies are the most common cause of food allergies and are responsible for 59% of deaths caused by food allergies (Kattan, Cocco, and Järvinen 2011; Pi et al. 2019). The prevalence of peanut allergies among children was estimated at approximately 2% (Savage and Johns 2015). As shown in Table 1, Ara h 1, Ara h 2, Ara h 3, and Ara h 6 are the major peanut allergens (Pi et al. 2021), which were recognized together by sera from 45% of patients with peanut allergies (Pi et al. 2019).

Recently, Zhou (2014) observed that the allergenicity of proteins was almost entirely diminished after peanut protein powder was fermented with *Bacillus subtilis* for 44 h. Further analyses showed that levels of Ara h 1 and Ara h 2 were significantly reduced, and the lipophilicity, hydrophilicity, emulsification and stability, foaming and stability, amount of water-soluble protein, and sensory flavor were all improved (Table 2). Pi et al. (2020) also found that the allergenicity of peanut protein was decreased, and the levels of polypeptide and soluble protein, as well as digestibility, were all increased after peanut pulp was fermented with *Bacillus natto*. He further determined that the reduction in α -helices was responsible for the reduction in allergenicity, as well as the increase in particle sizes in peanut protein after peanut pulp was fermented with *Bacillus natto* for 0-60 h (Pi et al. 2021). In addition, Maillard reactions occurred in the fermentation process, which changed the color of peanut protein from white to light yellow and might have had a minor effect on reducing the allergenicity of peanuts as well (Pi et al. 2021). Interestingly, peanut protein powder and peanut pulp were reduced by 28% and 75.4%, respectively, after fermentation with *Bacillus natto* for 36 h under the same conditions (Pi et al. 2021; Zhou 2014), further indicating that

some interactions, such as glycosylation and Maillard reactions, might occur to reduce protein allergenicity.

Milk

Milk is an excellent source of fat, proteins, minerals, and vitamins (Verhoeckx et al. 2015), significantly contributing to human health, especially in infants and young children (Villa et al. 2018). Unfortunately, milk allergies are the third most common food allergens, after only peanut and tree nuts (Kattan, Cocco, and Järvinen 2011; Villa et al. 2018). They account for 10%-19% of food allergies (Villa et al. 2018) and cause 8-15% of deaths due to food allergies (Kattan, Cocco, and Järvinen 2011). It has been reported that milk is the most common cause of food allergies in young children, followed by eggs (Manuyakorn and Tanpowpong 2019; Wiparat and Pornthep 2019), and it affects 2%-3% of the child population (Kattan, Cocco, and Järvinen 2011; Pescuma et al. 2011). Of note, the incidence of milk allergies in boys is higher than that in girls (Kattan, Cocco, and Järvinen 2011).

Milk contains at least 25 different proteins, including approximately 80% casein and 20% whey protein. Most, if not all, of these proteins may act as allergens (Ahtesh, Stojanovska, and Apostolopoulos 2018; Kattan, Cocco, and Järvinen 2011; Villa et al. 2018). The allergens are designated Bos d 2-13 (Table 1). Bos d 4, Bos d 5, Bos d 6, and Bos d 7 in whey protein account for 5%, 13%, 1.6%, and 0.4% of whole milk proteins, respectively (Ahtesh, Stojanovska, and Apostolopoulos 2018). Bos d 9, 10, 11 and 12 are casein proteins (Bos d 8) and represent ~ 32%, 10%, 28%, and 10% of the total milk protein, respectively (Kattan, Cocco, and Järvinen 2011; Villa et al. 2018). Bos d 5 and 9 are the leading causes of milk allergies in children (Kazemi et al. 2018; Prioult, Pecquet, and Fliss 2005). Bos d 5 is responsible for 80% of milk allergies in children and infants (Kazemi et al. 2018; Kleber, Weyrich, and Hinrichs 2006), largely due to its absence in human milk and its presence in cow's milk as a whey protein (Kleber, Weyrich, and Hinrichs 2006).

It has been estimated that approximately 82.4%, 13.6%, and 4.0% of the world's fresh milk comes from cows, buffaloes, and other sources (goats, sheep, and camels), respectively (Villa et al. 2018). The allergenicity of several fermentation milk samples was evaluated. Fermentation of skim milk from cow, buffalo, and goat milk with

Table 1. Common sources of major food allergens.

Food material	Allergen	Major Allergen	Biochemical name	Molecular Weight /kDa	Contents (% of total protein)	Recognize probability	References
Peanut	Ara h 1-Ara h 17 (Ara h 4 was renamed to Ara h 3.02)	Ara h 1 Ara h 2 Ara h 3	Cupin (Vicillin-type, 7S globulin) Conglutin (2S albumin) Cupin (Legumin-type, 11S globulin, Glycinin)	64 17 60, 37	12–16 10 3.7–4.3	95 95 95	(Pi et al. 2019; WHO/IUIS Allergen Nomenclature Subcommittee 2020)
	Bos d 2- Bos d 13	Ara h 6 Bos d 4 Bos d 5 Bos d 8	Conglutin (2S albumin) Alpha-lactalbumin Beta-lactoglobulin Caseins (for individual components see Bos d 9-Bos d 12)	15 14.2 18.3 20–30	6–9 5 13	95 27.6 50 46.5	
		Bos d 9 Bos d 10 Bos d 11	alphaS1-casein alphaS2-casein beta-casein	23.6 25.2 24	32 10 28	50 90 75	
Soy	Gly m 1- Gly m 8	Gly m 5 Gly m 6	Beta-conglycinin (vicilin, 7S globulin) Glycinin (legumin, 11S globulin)	see subunits see subunits	30 40	86 86	(Ahtesh, Stojanovska, and Apostolopoulos 2018; Biscola et al. 2018; Do, Williams, and Toomer 2016; Kattan, Cocco, and Järvinen 2011; Kazemi et al. 2018; Matsuo, Yokooji, and Taogoshi 2015; Shi et al. 2014; WHO/IUIS Allergen Nomenclature Subcommittee 2020; Villa et al. 2018) (Holzhauser et al. 2009; Kattan, Cocco, and Järvinen 2011; Sanjukta and Rai 2016; WHO/IUIS Allergen Nomenclature Subcommittee 2020; Yang et al. 2018) (Li et al. 2013; Matsuo, Yokooji, and Taogoshi 2015; WHO/IUIS Allergen Nomenclature Subcommittee 2020)
Egg	Gal d 1- Gal d 10	Gal d 1	Ovomucoid	28	11* of egg white protein	43.5	(Pasha et al. 2016; WHO/IUIS Allergen Nomenclature Subcommittee 2020)
		Gal d 2 Gal d 3 Gal d 4 Tri a 19 Tri a 20 Tri a 21	Ovalbumin Ovotransferrin Lysozyme C Omega-5 gliadin, seed storage protein Gamma gliadin Alpha-beta-gliadin	44 78 14 65 35 to 38	55* 12* 3* 69	52.1 13 36.9 47.6	
Wheat	Tri a 12, Tri a 14, Tri a 15, Tri a 17- Tri a 21, Tri a 25- Tri a 37, Tri a 39- Tri a 45	Jug r 1 Jug r 2 Jug r 3	2S albumin seed storage protein Vicilin seed storage protein Nonspecific lipid transfer protein type 1 (nsLTP1)	15–16 44 9		75 60 91.3	(Cox and Sicherer 2015; Geiselhart, Hoffmann-Sommergruber, and Bublin 2018; Masthoff et al. 2013; WHO/IUIS Allergen Nomenclature Subcommittee 2020; Weinberger and Sicherer 2018)
		Jug r 4	11S globulin seed storage protein	58.1		57	
Tree nut	Ana o 1- Ana o 3 in cashew	Jug r 5 Ana o 1 Ana o 2 Ana o 3 Pru du 3	PR-10 Vicilin-like protein Legumin-like protein 2S albumin Nonspecific lipid transfer protein 1	20 50 55 14 9		50 62 81	(Cox and Sicherer 2015; Geiselhart, Hoffmann-Sommergruber, and Bublin 2018; Masthoff et al. 2013; WHO/IUIS Allergen Nomenclature Subcommittee 2020; Weinberger and Sicherer 2018)
	Pru du 3- Pru du 8 and Pru du 10 in almond	Pru du 4 Pru du 5 Pru du 6	Profilin 60 s acidic ribosomal prot. P2 Amandin, 11S globulin legumin-like protein	14 10 360	65–75%	44 50	
	Cor a 1, Cor a 2, Cor a 6, Cor a 8- Cor a 15 in hazelnut	Cor a 1	Pathogenesis-related protein, PR-10, Bet v 1 family member	17		100	
		Cor a 2, Cor a 8, Cor a 9	Profilin Nonspecific lipid transfer protein type 1 11S seed storage globulin (legumin-like)	14 9 40		15.4 100 86	

(continued)

Table 1. Continued.

Food material	Allergen	Major Allergen	Biochemical name	Molecular Weight /kDa	Contents (% of total protein)	Recognize probability	References
Shellfish	Ber e 1 and Ber e 2 in brazil	Cor a 11	7S seed storage globulin (vicilin-like)	48		43-47	(Ruethers et al. 2018; WHO/IUIS Allergen Nomenclature Subcommittee 2020; Thalayasingam and Lee 2015; Wong, Tham, and Lee 2019)
		Cor a 12	17 kDa oleosin	17		63.8	
		Cor a 13	14-16 kDa oleosin	14-16		63.8	
		Cor a 14	2S albumin	10		33.3	
		Ber e 1	2S sulfur-rich seed storage albumin	9		100	
	Car i 1, Car i 2, and Car i 4 in pecan	Ber e 2	11S globulin seed storage protein	29		56	
		Car i 1	2S albumin seed storage protein	16		79	
		Car i 4	Legumin seed storage protein	55.4		59	
		Pis v 1	2S albumin	7		68	
		Pis v 2	11S globulin subunit	32		50	
	Pin p 1 in Pine pen m 1- pen m 4 and pen m 6 in Penaeus monodon	Pis v 3	Vicillin	55		37	
		Pis v 5	11S globulin subunit	36		36	
		Pin p 1	2S albumin	6.15		75	
		pen m 1	tropomyosin	38		69 in shrimp	
		pen m 2	Arginine kinase	40		100	
Fish	Lit v 1- Lit v 4 in Litopennaeus vannamei	pen m 3	Myosin light chain 2	20		82	(Sharp and Lopata 2014; WHO/IUIS Allergen Nomenclature Subcommittee 2020; Thalayasingam and Lee 2015)
		pen m 4	Sarcoplasmic calcium binding protein	20		50	
		Lit v 1	Tropomyosin	36		100 in shrimp	
		Lit v 2	Arginine kinase	40		100	
		Lit v 3	Myosin light chain 2	20		55	
	Pen a 1 in Penaeus aztecus	Lit v 4	Sarcoplasmic calcium binding protein	20		60	
		Pen a 1	Tropomyosin	36		85 in shrimp	
		Cra g 1	Tropomyosin	38		50 in shellfish	
		Hal m 1		49		29 in haliotis midae	
		Hel as 1	Tropomyosin	36		18 in brown garden Snail	
	Tod p 1 in garden snail todarodes pacificus	Tod p 1	Tropomyosin	38		100 in shrimp	
		Gad c 1	Beta-parvalbumin	12		90 in fish	
		Sal s 1	Beta-parvalbumin 1	12		63.6 in cod	
		Atlantic salmon					
	Gad m 1- Gad m 3 in Atlantic cod	Gad m 1	Beta-parvalbumin	12		100 in cod	

Table 2. Effect of fermentation on the allergenicity and physicochemical properties in common food allergens.

Food Material	Strains for fermentation	Alteration of allergenicity	Changes in physicochemical properties	Reference
Peanut	<i>Bacillus subtilis</i>	Reduced by 100% (total protein)	Lipophilicity, hydrophilicity, emulsification and its stability, foaming and its stability, the content of water-soluble protein, the sensory flavor was improved	(Zhou 2014)
	<i>Bacillus natto</i>	Reduced	Contents of polypeptide and soluble protein, as well as digestibility were increased	(Pi et al. 2020)
Milk	<i>Bacillus natto</i>	Reduced	Particle sizes increased	(Pi et al. 2021)
	<i>L. rhamnosus</i> GG	Reduced	Content of free amino groups increased 3 times	(Yao et al. 2014)
	<i>Lactobacillus casei</i> 1134	Reduced	Content of free amino acid increased 3.35 times	(Yao et al. 2015)
	<i>Lactobacillus casei</i>	Reduced	Content of free amino acid increased 1.5 times	(Shi et al. 2014)
	<i>Lactobacillus acidophilus</i> CRL 636	the allergenicity of Bos d 5 was reduced	Digestibility of Bos d 5 by pepsin increased 7.275 times	(Pescuma et al. 2009)
Soy	<i>B. subtilis</i> KCCM11438P	Reduced	Digestibility and nutritional quality increased	(Seo and Cho 2016)
	<i>Lactobacillus helveticus</i>	Reduced by 100%	Water- and oil-binding capacity, protein solubility at pH 4.0 and foaming activity were increased. bitter and beany off-flavors were decreased	(Meinlschmidt et al. 2016)
	<i>Neurospora crassa</i>	Reduced	Free amino acids increased 13times, vitro digestion rate of protein increased by 37.97%	(Li et al. 2019)
Egg	<i>Lactic acid bacteria</i>	The allergenicity of egg white was reduced by 30%-61%	Taste, flavor and texture was improved	(Nie 2011)
	<i>Lactobacillus delbrueckii</i>	The allergenicity of egg white was reduced	Amino nitrogen content increased by 30%	(Li et al. 2013)
Wheat	<i>Lactic acid bacteria</i>	Reduced	No reported	(Leszczyńska et al. 2012; Stefańska et al. 2016)
Tree nuts (cashew)	<i>Quinoa-Based Rejuvelac Starter Culture</i>	Reduced	Nutritional composition retained	(Chen et al. 2020)
Shellfish	Salted-fermented	Reduced	No reported	(Hong et al. 2003)
Fish	<i>staphylococcus xylosus</i>	Reduced by 22.3%	Digestibility increased	(Gao et al. 2017)

Lactobacillus helveticus, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and a cocultivation of *Lactobacillus delbrueckii* subsp. *bulgaricus* with *Streptococcus thermophilus* led to a reduction in allergenicity in cow milk (98.55%, 34.18%, and 98.48%, respectively), buffalo milk (45.32%, 91.09%, and Nd, respectively), and goat milk (97.92%, 100%, and 100%, respectively) compared to unfermented cow, buffalo, or goat milk (Anggraini, Tongkhao, and Chanput 2018). Differences in allergenicity reduction under the same fermentation conditions indicated that the structure and epitopes of milk allergens varied among the types of milk.

At present, cow milk allergies are responsible for milk allergies, and *Lactobacillus* is the most common strain for fermentation of cow milk. A previous study conducted by Jedrychowski et al. revealed that *Lactobacillus* fermentation reduced the antigenicity of whey proteins in sterilized cow's milk by > 99% after screening lactic acid bacteria (399 meso- and thermophilic strains or mixed cultures) for their ability to reduce the antigenicity of Bos d 4 and 5 (Jedrychowski 1999). It was also reported that the allergenicity of Bos d 4 and 5 was reduced after fermentation with *Lactobacillus casei* LcY, and an even greater decrease was observed after three-stage simulated digestion (Wróblewska

et al. 2016). The allergenicity reduction of Bos d 4 and 5 in cow's milk after *Lactobacillus* fermentation resulted from the proteolytic activity of *Lactobacillus* on Bos d 4 and 5 (Kazemi et al. 2018; Wróblewska et al. 2016; Zheng et al. 2014). Moreover, *Lactobacillus* has proteolytic activity against α -casein, β -casein, κ -casein, bovine serum albumin, and lactoferrin, resulting in reducing their immunoreactivity (Wróblewska et al. 2016). A similar result was found in other bacteria. For example, competitive ELISA showed that the proteolytic activity of *Enterococcus faecalis* VB63F was responsible for the degradation of Bos d 9-11 and reduction of allergenicity of bovine milk proteins in fermentation (Biscola et al. 2016). An in vitro experiment conducted by Wróblewska, et al. treated Bos d 4/5-immunized mice with probiotic bacteria fermentation whey products and found a reduction in allergy marker levels (IL-4, IgE, and specific IgG1) and an increase in the main regulatory cytokines (IL-10 and TGF- β), resulting in an altered Th1/Th2 balance toward a Th1 response, modulating the immune response and reducing responsiveness to milk allergens (Wróblewska et al. 2019).

Fermentation also affects the physicochemical properties of milk. As shown in Figure 2, while IgE binding and the

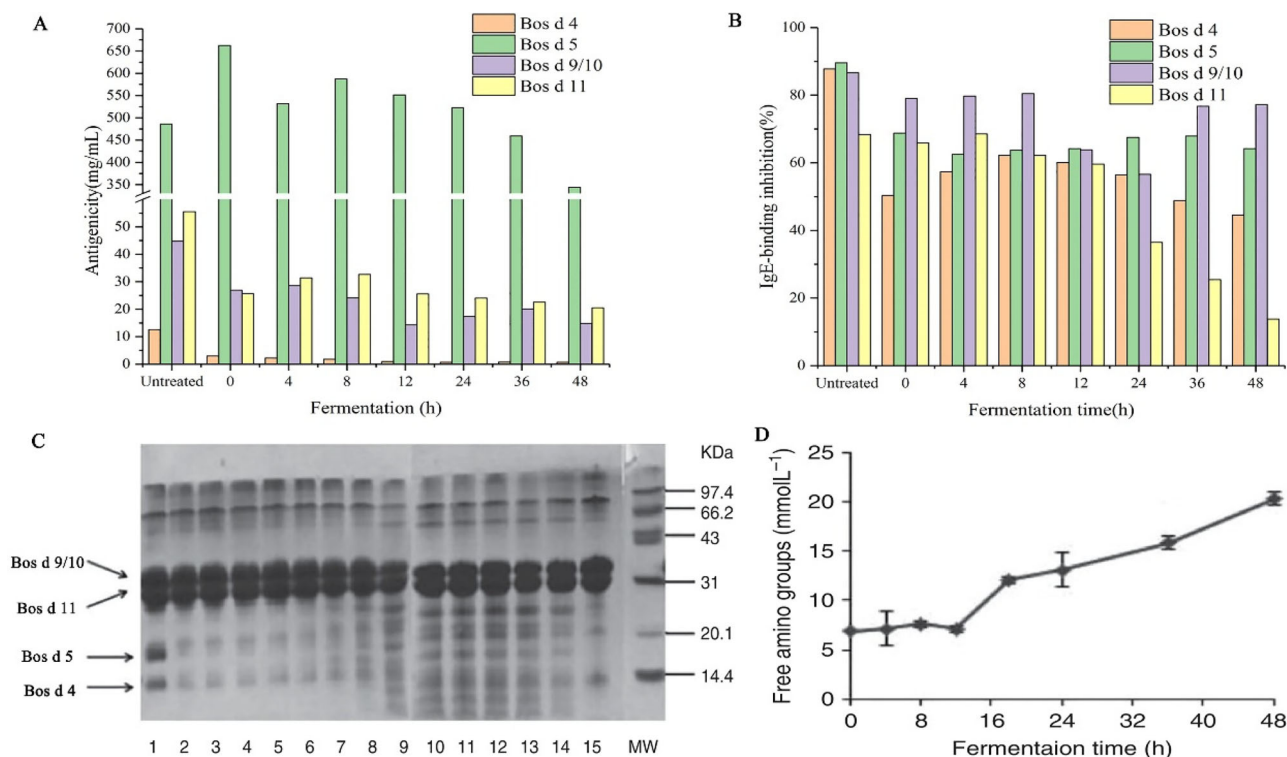


Figure 2. The effect of fermentation with *Lactobacillus rhamnosus* GG on cow's milk (Yao et al. 2014). **A.** Effect of fermentation on the antigenicity. **B.** Effect of fermentation on the IgE-binding inhibitions. **C.** SDS-PAGE analysis of milk proteins during fermentation. Lane 1: unheated milk; lane 2: unfermented milk; lanes 2–15: fermented milk at different fermentation time (0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 36, 48 h); MW: molecular weight markers. **D.** Evolution of free amino groups in the reconstituted skimmed milk during the fermentation.

amounts of major allergens were markedly reduced by fermentation with *Lactobacillus rhamnosus* GG, the amounts of free amino groups increased approximately 3-fold (Yao et al. 2014). Similar results were found in skimmed milk fermented with *Lactobacillus casei* (Shi et al. 2014; Yao et al. 2015). Pescuma et al. further demonstrated that *Lactobacillus acidophilus* CRL 636 was able to hydrolyze 52% of Bos d 5, resulting in the destruction of its primary epitopes (41-60, 102-124, and 149-162). Meanwhile, the digestibility of Bos d 5 by pepsin increased 7.275-fold (Pescuma et al. 2009).

Soy

Soy includes soybeans, black beans, chickpeas, and green beans, which are used to make popular products, such as natto, douchi, and tungrymbai (Sanjukta and Rai 2016). Soybean meal is one of most important protein sources in China (Li et al. 2019) because of its high-quality protein, wide availability, and low cost (Yang et al. 2018). Soy contains a high level of proteins (43%–48% (w/w)) that possess balanced amino acid compositions and lysine (2.5%~2.8%) (Li et al. 2019). The active components in soy also offer benefits, such as cholesterol reduction, antioxidant activity, cancer, and diabetes prevention (Biscola et al. 2017).

It has been estimated that soy allergies affect 0.4% of young children (Kattan, Cocco, and Järvinen 2011). Currently, 8 soy allergens, Gly m 1- 8, have been identified (Table 1), accounting for approximately 30% of defatted

soybean meal (Chi and Cho 2016). Gly m 5 and 6 are the major soy allergens, and sensitivity to them is an indication of severe allergic reactions to soy (Holzhauser et al. 2009).

It has been reported that the allergenicity of Gly m 5 and 6 in soymilk, soybean flour, and soybean meal was significantly reduced after fermentation (Bao et al. 2014; Biscola et al. 2017; Yang et al. 2018). Similar results were found in soy sauce, in which soybean allergens were gradually degraded during the fermentation process (Kobayashi and Taniuchi 2018; Magishi et al. 2017). A recent study conducted by Yang et al. found that *Bacillus subtilis* was more favorable than other microorganisms for developing hypoallergenic soybean products due to the highest reduction (44.53%) in allergenicity of soybean meal after *Bacillus subtilis* fermentation compared to *Lactobacillus plantarum*, *Lactobacillus casei*, *Bacillus licheniformis* and *Aspergillus oryzae* (Yang et al. 2020). However, for different states of soybeans, such as soybean flour, a different result was found. Bao et al. found the highest reduction in reactivity to the anti-Gly m 5 antibody, up to 93%, 85%, 100%, 80%, 85%, 58%, 100%, 83%, 95%, and 94%, when soybean flour was separately fermented with one of 10 microorganisms (*Bacillus subtilis* subsp. *spizizenii*, *Bacillus licheniformis*, *Bifidobacterium breve*, *Bifidobacterium animalis*, *Bifidobacterium longum*, *Aspergillus oryzae*, *Aspergillus niger*, *Lactobacillus fermentum*, *Saccharomyces cerevisiae*, and S-8, respectively) (Bao et al. 2014). These results revealed that the selection of microorganism types and raw material status play an important role in developing hypoallergenic soybean products.

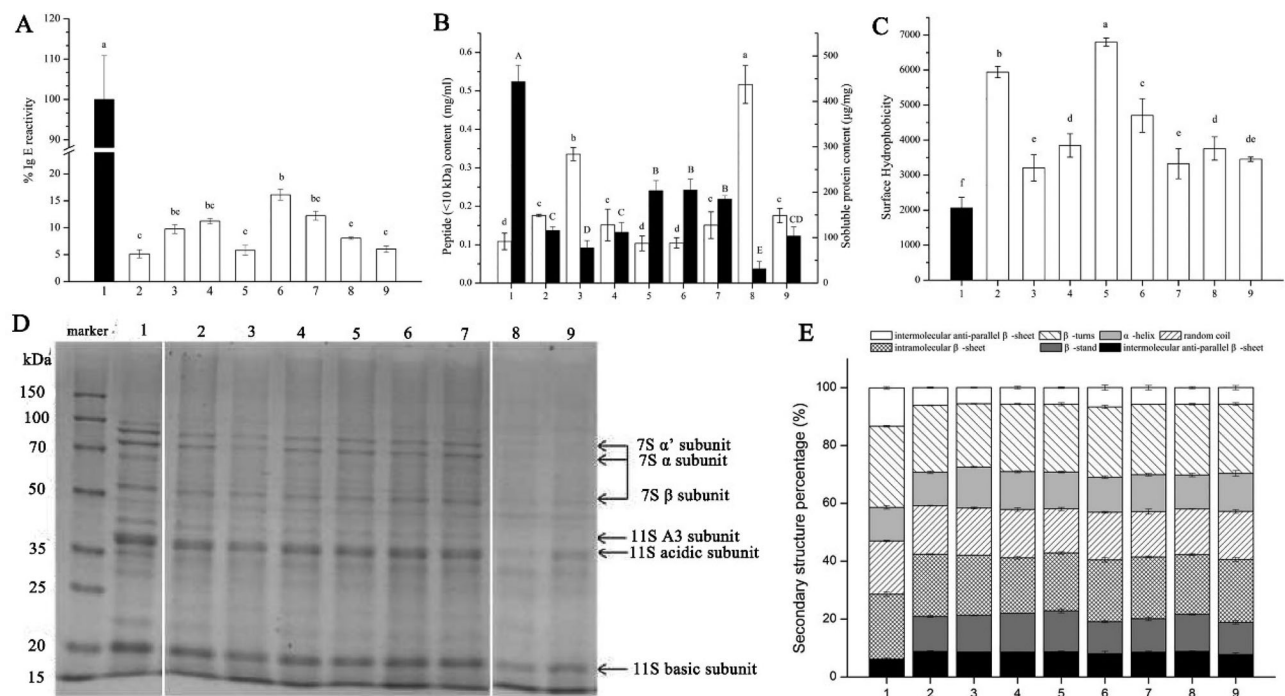


Figure 3. The effect of *Lactobacillus plantarum* fermentation on soy protein (Rui et al. 2019). 1: soy protein isolates, 2-9: soy protein isolates fermented by *Lactobacillus plantarum*-ZR, -Y-1, -MB1-6, -L3-4, -70810, -M'-6, -B1-6, and -Dong. A. IgE reactivity. B. Peptide (<10 kDa) and soluble protein content, different patterns represented the peptide content (white), and soluble protein content (black). C. Surface hydrophobicity. D. SDS-PAGE. E. Secondary structure.

Structural analysis showed that the increase in surface hydrophobicity and β -strands was responsible for 83.8%–94.8% allergenicity reduction of soy proteins after fermentation with *Lactobacillus plantarum* (Figure 3). In addition, the levels of low molecular weight proteins and polypeptides (<10 kDa) content, except for *L. plantarum*-derived L3-4 and 70810, were markedly increased after fermentation due to the reduction (53.8%–92.8%) in soluble proteins, including β -conglycinin and glycinin (Rui et al. 2019). Therefore, degradation of allergen proteins and changes in conformational structure were key factors for reducing allergenicity. A BALB/c mouse model experiment further evaluated whether fermented *Lactobacillus* soymilk decreased levels of Th2-related cytokines, serum allergen-specific IgG/IgE, and plasma histamine and increased IFN- γ production, resulting in a Th1/Th2 balance and reduced allergenicity (Xia et al. 2019). Thus, fermentation can balance Th1/Th2 to reduce soy allergenicity in vivo, in agreement with the milk allergy mouse model (Wróblewska et al. 2019).

Interestingly, along with the reduction in allergenicity, the digestibility and nutritional quality of soybean meal are also improved after fermentation with *B. subtilis* KCCM11438P (Seo and Cho 2016) and *Neurospora crassa* (Li et al. 2019). Similarly, along with the reduction in allergenicity, fermentation with *Lactobacillus helveticus* increased the water- and oil-binding capacity, protein solubility at pH 4.0 and foaming activity, and decreased bitter and beany off-flavors (Meinschmidt et al. 2016). Further analysis demonstrated that fermentation with *Neurospora crassa* led to 10.05% protein hydrolysis, a 13-fold increase in free amino acids, and a 37.97% elevation in the in vitro digestion rate of proteins (Li et al. 2019).

Therefore, fermentation reduces the allergenicity of soy due to the degradation of allergens, the change in protein structure and the Th1/Th2 balance, simultaneously changing its physiochemical properties.

Egg

Egg allergies are the second most common childhood food allergy (Li et al. 2013), affecting 1.6–3.2% of the total child population (Li et al. 2013). The allergens Gal d 1–4 are from egg white proteins (Li et al. 2013), whereas Gal d 5–6 are from egg yolk (Matsuo, Yokooji, and Taogoshi 2015). In general, the allergenicity of egg white is higher than that of egg yolk (Verhoeckx et al. 2015).

It has been reported that the allergenicity of egg white was reduced by 61%, 35%, and 30% after fermentation with lactic acid bacteria A, B, and C, respectively. Fermentation also improved taste, flavor and texture (Nie 2011). Further analyses revealed that the 50% reduction in egg white allergenicity after fermentation with *Lactobacilli delbrueckii* was due to a reduction in 238 Da ovomucoid. There was also an ~30% increase in amino nitrogen levels, indicative of extensive protein hydrolysis (Li et al. 2013).

Wheat

Wheat is rich in amino acids, vitamins, and trace elements. It has been developed as the basic ingredient of food products, such as baked goods, pasta, and pizzas (Stefańska et al. 2016), which make it a staple food for most of the world's population (Iweala, Choudhary, and Commings 2018). Wheat contains 10–14% proteins (Verhoeckx et al. 2015), 20% of

which are soluble (albumin and globulin) and 80% of which are insoluble (gliadin and glutenin) (Pasha et al. 2016).

Wheat allergies are the third most common cause of food allergies in children (Pasha et al. 2016), affecting 0.4%-1% of children (Corinne A. Keet et al. 2009). Among wheat allergens (Table 1), Tri a 19 has the highest specificity for diagnosing wheat allergies, especially in allergic children (Pacharn and Vichyanond 2017).

It was reported that the allergenicity and allergen content of wheat were decreased after treatment with probiotic proteases (De et al. 2007; Greco et al. 2011) and fermentation extract (Ko et al. 2010). Wheat is the primary raw ingredient of soy sauce, and wheat allergens are completely degraded into amino acids and peptides that lose their IgE-binding ability during the fermentation process (Kobayashi and Taniuchi 2018). Similar to milk, *Lactobacillus* is also common for fermentation of wheat. Leszczyńska et al. (2012) found that lactic acid fermentation reduced the allergenicity of wheat proteins by up to 60%. Fu, Xie, et al. (2020) isolated twelve strains of lactic acid bacteria and yeast from sourdough and found that *Pediococcus acidilactici* XZ31 showed higher proteolytic activity on wheat protein substrates, resulting in a significant reduction in wheat protein. Mecherfi et al. (2019) evaluated that fermentation of gluten by *Lactococcus Lactis* induced a reduction in antigenicity and allergenicity because lactic acid bacteria hydrolyzed the total gliadin repetitive domain, which contained the main epitopes responsible for wheat allergy. Similar studies also showed that lactic acid bacteria strains had a strong capacity for proteolytic degradation of wheat proteins, resulting in the destruction of IgE-binding epitopes of wheat allergens and a reduction in wheat allergies (Rizzello et al. 2006; Stefańska et al. 2016).

Tree nuts

Tree nuts are rich in unsaturated fats, phenolics, phytosterols, tocopherols, minerals, and fiber (Verhoeckx et al. 2015) and exert various beneficial effects, including antioxidant, antimutagenic and anticarcinogenic effects (Atanasov et al. 2018; Vanga and Raghavan 2017). Tree nuts are the second most common cause of food allergies (Kattan, Cocco, and Järvinen 2011; Villa et al. 2018), affecting 1.2-2% of the global population (Vanga and Raghavan 2017) and are responsible for 31% of deaths caused by food allergies (Vanga and Raghavan 2017). Of note, tree nuts are the fourth most common cause of food allergies in children. Nine nuts account for the majority of allergies to tree nuts, including walnut (22% of the patients allergic to tree nuts), almond (13.2-15%), pistachio (10%), cashew (15.5%), pecan (14%), hazelnut (7.5%), macadamia (9%), Brazil (10%), and pine (5%) (Cox and Sicherer 2015; Vanga and Raghavan 2017; Weinberger and Sicherer 2018). Major tree nut allergens belong to the protein families 2S albumins, vicilins, legumins, and nonspecific lipid transfer proteins (Geiselhart, Hoffmann-Sommergruber, and Bublin 2018), which are listed in Table 1.

At present, there are a few reports concerning the effects of fermentation on the allergenicity of various tree nuts. It was reported that the allergenicity of cashews was reduced after fermentation with quinoa-based *rejuvelac* starter culture. The reduction in cashew allergens might be due to proteolytic cleavage by a bioactive molecule produced during fermentation. In addition, cashews retain their nutritional composition after fermentation (Chen et al. 2020)

Shellfish

The shellfish group primarily includes crustaceans (shrimp, crab, lobster, and crawfish) and mollusks (limpet, snail, abalone, clam, oyster, scallop, mussel, squid, and octopus) (Fang et al. 2018), which reportedly cause 3.8% and 1.6%, respectively, of food-induced allergic reactions in Spanish children (Ayuso 2011). Generally, the prevalence of shellfish allergies in children and men is significantly lower than that in adults and women (Ayuso 2011).

Crustacean allergies are more common than mollusk allergies, with shrimp being the most common cause of shellfish allergies (Wong, Tham, and Lee 2019). Many investigations have shown that tropomyosin, arginine kinase, myosin light chain, and sarcoplasmic calcium-binding protein are the major shrimp allergens (Ayuso 2011) and are recognized by 72–100%, 10–51%, 19 to 55%, and 29–50% of shrimp-allergic patients, respectively (Ruethers et al. 2018; Sub-Committee., 2020).

It has been shown that the allergenicity of salt-fermented shrimp was markedly reduced, indicating that fermentation may decrease the allergenicity of shrimp (Hong et al. 2003). Interestingly, it was reported that oral administration of *Lactobacillus casei* attenuated allergy symptoms and reduced intestinal epithelial damage in BALB/c mice allergic to tropomyosin (Fu, Xie, et al. 2020).

Fish

Fish are an important protein-rich food that provides a good combination of amino acids meeting human nutritional requirements and are also beneficial for human health in many different ways, including reducing plasma cholesterol levels and providing cardiovascular protection (Tahergorabi, Hosseini, and Jaczynski 2011). The prevalence of fish allergies ranges from 0.2 to 2.29% in the general population but can reach up to 8% in fish processing workers (Sharp and Lopata 2014). It has been reported that the four most common fish species causing IgE-mediated allergic reactions are hake (24.8% of fish allergies), yellowtail (21.9%), salmon (15.2%), and mackerel (15.2%) in South Africa (Sharp and Lopata 2014).

Identified fish allergens include parvalbumin, hormone vitellogenin, collagen, gelatin, and muscle proteins. Among them, β parvalbumin is recognized by 90% of patients allergic to fish (Sharp and Lopata 2014). Interestingly, it was found that the allergenicity of parvalbumin was reduced by 22.3% after *Lateolabrax japonicus* was fermented with

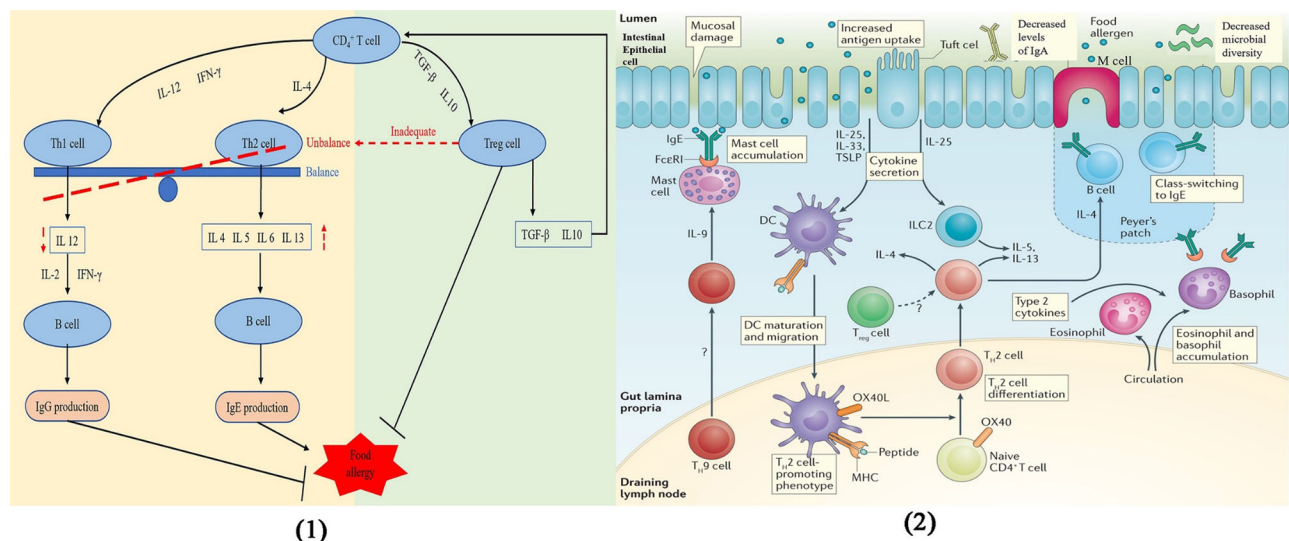


Figure 4. (1) Th1/Th2 balance and allergenic reaction. When the body was exposed to food allergens and has inadequate regulator T cells (Treg) which suppress food allergy reaction, the excessive activation of Th2 will lead to the secretion of Th2 cytokines such as IL-4 and IL-5, resulting in the production of more allergic IgE antibodies that causes the allergic symptoms (Wang et al. 2019) (2) Th2 cell-mediated inflammatory response to oral antigen in the gut. When food allergens pass the intestinal epithelium, the broke down of tolerance to food allergens induces the accumulation of mast cell, Th2 cell, eosinophil and basophil, resulting in the production of mediator and IgE, which lead to the clinical symptoms of allergy such as urticarial, rhinitis, and swelling, and pathological manifestations such as low level of IgA, Epithelial damage and low microbial diversity (Yu, Freeland, and Nadeau 2016).

Staphylococcus xylosus for 60 h (Gao et al. 2017), largely due to the degradation of parvalbumin by pepsin.

The mechanism of fermentation-mediated reductions in food allergies

A lack of immunologic and clinical tolerance to food allergens leads to food allergies (Barni et al. 2020), which generally occur within 2 h of exposure to allergens (Manuyakorn and Tanpowpong 2019; Wiparat and Pornthep 2019). As shown in Figure 4, pathological manifestations of allergic patients are as follows: 1) a lack of Treg cells, which is essential for maintaining tolerance against allergens in early-life exposure to allergens (Perdijk and Marsland 2019); 2) excessive activation of Th2, leading to an imbalance of Th1/Th2 (Wang et al. 2019); 3) a low level of IgA (Abdel-Gadir et al. 2019); 4) epithelial damage (Xia et al. 2019; Yu, Freeland, and Nadeau 2016); and 5) low microbial diversity (Fujimura and Lynch 2015).

Fermentation is a favorable way to alleviate food allergies because it reduces the allergenicity of allergens, and its strains/metabolites can decrease human sensitization to food allergens, resulting in mitigating the pathological manifestations in allergic patients.

With respect to food allergens (Figure 5), 1) food allergen content and epitopes were reduced or destroyed due to proteolysis and acid-induced denaturation during fermentation (Rui et al. 2019); and 2) glycosylation and Maillard reactions that occurred during fermentation reduced the allergenicity of food allergens (Pi et al. 2019). However, the contribution of the Maillard reaction sometimes increased the allergenicity of the entire peanut extract, as well as Ara h 1 and Ara 2 during the process of roasting (Chung and Champagne 2001; Maleki et al. 2000). Chung and Champagne (2001) further found that the higher the level of AGEs (advanced

glycation end products) in roasted peanuts, the higher the IgE binding capacity. Therefore, levels of AGEs must be strictly controlled by changing the processing conditions (e.g., strain, temperature, and time) during the fermentation process. 3) The content of allergens in food was decreased because some allergens were released into the water (Pi et al. 2019). Of note, fermentation directly affects food allergens through mechanisms 1-3, among which reason 1 is considered to be the primary effect.

With respect to fermentation strains, mouse model experiments have revealed that oral administration of *Lactobacillus pentosus* S-PT84 attenuated OVA-induced allergic responses by balancing the Th1/Th2 response, downregulating Th-17 cells, increasing the generation of T-reg cells, suppressing histamine release, and modulating mast cells (Majumder et al. 2020), that oral application of *Lactobacillus casei* attenuated tropomyosin-induced allergic responses because of the reduction in intestinal epithelial damage (Fu, Xie, et al. 2020), and that oral intake of *Lactobacillus murinus* attenuated ovalbumin-induced allergic responses by restoring the deteriorated profile of enteric flora and suppressing the elevated nonspecific bacteria associated with ovalbumin allergies (Huang et al. 2016). Moreover, oral administration of *Lactobacillus murinus* increased levels of fecal IgA in healthy dogs, indicating a potential effect of *Lactobacillus murinus* on food allergies (Luis et al. 2014). Colonization with Clostridia species increased the expression of IL-22, a barrier-promoting cytokine, resulting in decreased intestinal permeability and reduced uptake of peanut proteins into the serum (Blazquez and Berin 2017).

Fermentation metabolites, similar to fermentation strains, can also modulate the immune system by regulating proliferation and cytokines release from T cells, Th 17 cells, and Treg cells (Dargahi et al. 2019). For example, short-chain

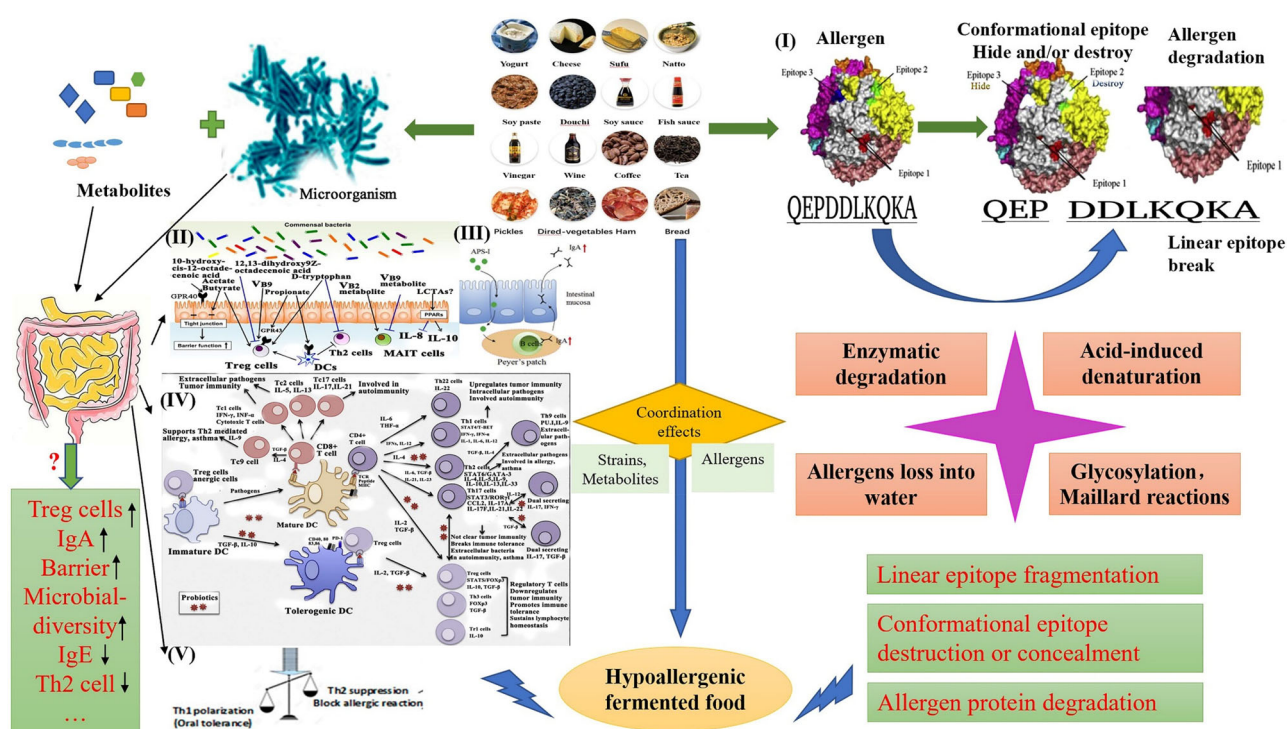


Figure 5. The mechanism of fermentation for reducing food allergy. Allergen was degraded by four effects, resulting in the reduction of allergenicity in food allergens. Allergen structure chart (I) was from (Pi et al. 2019). Bacteria and its metabolites may induce the increase of Treg cells, epithelial barrier function, the level of IgA and bacterial diversity, and the inhibition Th2 generation and activation Th1 response, resulting in the reduction of IgE and the relief of allergy. (II) Bacterial metabolites on regulating immune responses for the allergic diseases (Hirata and Kunisawa 2017). (III) The acidic polysaccharide APS-I, isolated from soy Sauce, crossed the murine intestinal epithelium to induces IgA production. (Cao et al. 2019). (IV) Immunomodulatory effects of probiotics stimulating T helper (Th)-1, Th2, Th17 cells or T regulatory (Treg) cells (Dargahi et al. 2019). (V) Bacterial and its metabolites regulating the balance of Th1/Th2 response (El Mecherfi, et al., 2020).

fatty acids (acetate, propionate, and butyrate) increase the induction of Tregs (Hirata and Kunisawa 2017). Propionate acts on dendritic cells (DCs) to produce TGF- β and retinoic acid, which induce the conversion of naive T cells to Tregs and inhibit Th2 generation (Hirata and Kunisawa 2017). D-tryptophan and propionate act through the GPR41 receptor to suppress Th2 induction (Hirata and Kunisawa 2017). The acidic polysaccharide APS-I, isolated from soy sauce, appears to cross the murine intestinal epithelium, where it induces intestinal secretory IgA production (Cao et al. 2019). The metabolites 10-hydroxycis-12-octadecenoic acid and a linoleic acid-derived metabolite enhance epithelial barrier function, which reduces levels of food allergens in the systemic circulation (Hirata and Kunisawa 2017).

In conclusion, bacteria and their metabolites reduce human sensitization to food allergens by inducing Tregs, regulating the balance of the Th1/Th2 response, enhancing epithelial barrier function to decrease allergen uptake into the systemic circulation, and increasing both levels of IgA and bacterial diversity (Figure 5).

Discussion and conclusions

Fermentation markedly reduces the allergenicity of food at a low cost and does not use any additional chemicals. It is also a safe application that may improve sensory properties (Rui et al. 2019), stability (Serrazanetti et al. 2013), digestibility (Yuan et al. 2017), and nutritive value (Yuan et al. 2017). Compared to other methods for reducing food

allergies, fermentation has additional advantages, including improving nutritive value, maintaining healthy human intestinal flora, balancing Th1/Th2 responses, and enhancing the intestinal barrier (Keet and Allen 2018; Kirilov et al. 2009). However, the effect of fermentation on food allergenicity is dependent on the type of microorganism and processing conditions, such as temperature, pH, and substrate concentration. Bacteria differ in their activity (Wróblewska et al. 2019), and not all probiotics are equally efficient at inhibiting the allergic response (Ai et al. 2015). Wróblewska et al. (2016) even found that two protein fractions (cyclopropane-fatty-acyl-phospholipid synthase and carboxylate-amine ligase) of *Lactobacillus casei* LcY cells in fermented buttermilk were able to bind to human IgE in milk allergic patients. Kobayashi & Taniuchi. (2018) and Magishi et al. (2017) found that soybean allergens in soy sauce were gradually degraded during the fermentation process but were not completely degraded in raw soy sauce. In addition, fermentation does not always eliminate the allergenicity of milk (Kleber, Weyrich, and Hinrichs 2006) and wheat (Fu, Xie, et al. 2020). In addition, fermentation may produce bitter peptides, resulting in degradation of taste. Therefore, the selection of strains and processing conditions appears to be important to alleviate food allergenicity.

It has been reported that autoclaves, heat treatment, and enzymatic hydrolysis are effective for assisting fermentation to reduce allergens in peanuts, soy, and milk (Anggraini, Tongkhao, and Chanput 2018; Pi et al. 2019). Kobayashi and Taniuchi (2018) and Magishi et al. (2017) found that

heat treatment, sedimentation, and filtration are very important processes in addition to enzymatic degradation to completely reduce the allergenicity of soy sauce during its fermentation. Therefore, a combination of different processing techniques in conjunction with fermentation may provide novel avenues to reduce the allergenicity of food.

Of note, fermentation with multiple microbe strains might represent another effective strategy. It was reported that the greatest reduction in the antigenicity of Bos d 4 (88%) and 5 (91%) was achieved after milk was fermented with a combination of *L. helveticus* and *S. thermophilus* compared to fermentation with either strain alone (Bu et al. 2010). Similar results were observed in independent studies (Chen et al. 2011; Leszczyńska et al. 2009). Thus, identifying compatible mixed strain fermentation is another promising strategy for reducing food allergens and allergies.

Moreover, some fermented food may alleviate other food allergies. It was reported that oral administration of fermented red ginseng alleviated ovalbumin-induced allergic responses in mice (Kim et al. 2019; Lee et al. 2012), which was more effective than oral administration of red ginseng (Lee et al. 2012). In addition, animals and plants contain a variety of antiallergic substances (Wang et al. 2019), and their activity may be increased by fermentation. It was indicated that fermented food without allergens also prevented food allergies, representing a promising treatment for food allergies.

In conclusion, it is conceivable that a combination of mixed strain fermentation with additional processing, such as heat treatment, pulsed light, and ultrasonication, represents a new trend for reducing the allergenicity of various foods, and fermenting food is a promising treatment for food allergies.

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No potential conflict of interest was reported by the authors.

Authors' contributions

Xiaowen Pi designed the manuscript, performed preliminary data analysis, and wrote the initial review. Professor Yili Yang proofread of the manuscripts, including grammar and content. Professor Yuxue Sun discussed with "Xiaowen Pi" and helped "Xiaowen Pi" to modify manuscripts. Professor Xibo Wang, Yin Wan, Guiming Fu, Hongbing Chen suggested some amendments to the initial review. Professor Jianjun Cheng supervised the project and edited the final version of the manuscript.

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